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Podophyllotoxin and antitumor synthetic aryltetralines. Toward a biomimetic preparation

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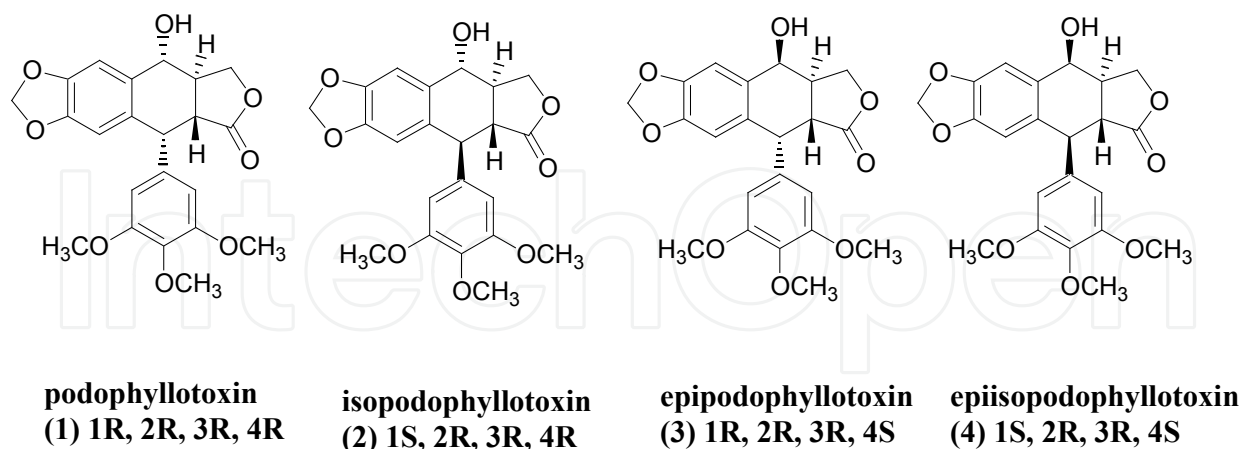
1. Introduction

Organic compounds obtained from radical coupling of phenylpropenoidic phenols have an important biological role. In fact, they constitute organic polymers such as lignin (Higuchi, 1985) lignans (Ayers & Loike, 1990), suberin (Berdards et al. 1995) and algal cell walls (Ragan, 1984). To date, several hundreds of these lignans have been isolated. Whilst their biological role in plants is unclear and remains to be fully elucidated, they have been shown to display a substantial range of biological activity and have a long and fascinating medical history that emanates from their use as folk remedies to treat an assortment of conditions (Bett, 1951). They are typically dimers and their primary physiological role in plants is in plant defense (Beutner & Ferenczy, 1997). Some lignans have found application in medicine, such as podophyllotoxin in venereal wart treatment (Meresse et al, 2004), or its semisynthetic derivatives etoposide, and teniposide in cancer therapies (Ward, 1997).

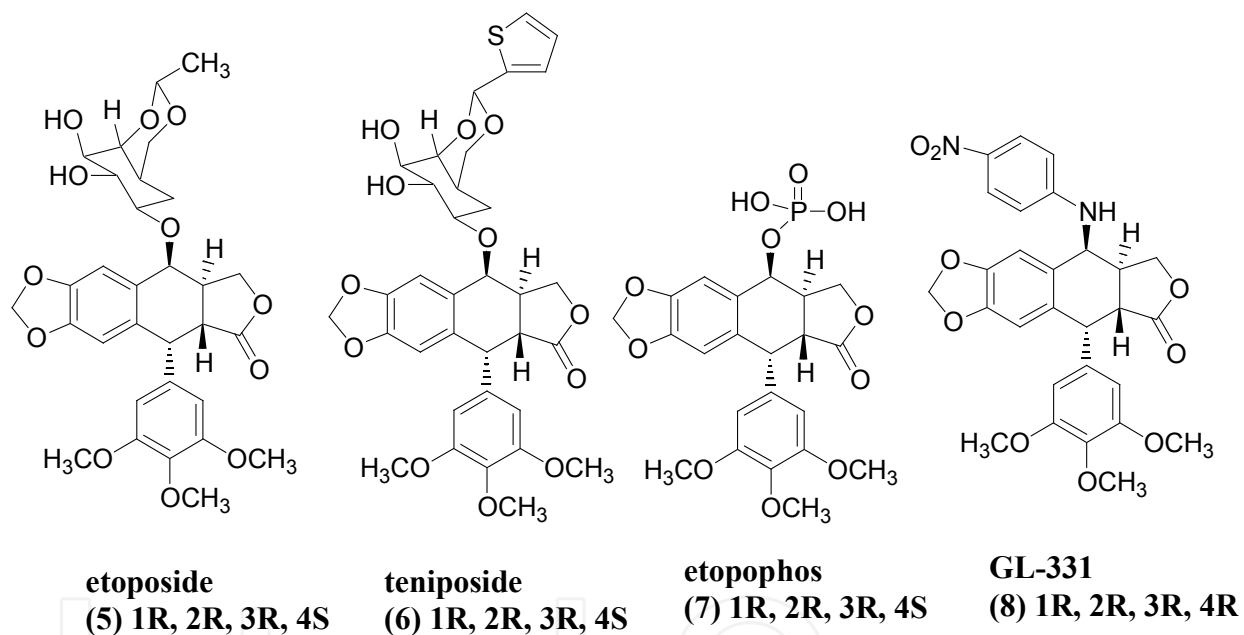
2. Aryltetraline lignans

Aryltetralin lignans are lead substances for the semi-synthetic anticancer derivatives etoposide, teniposide and etopophos (Ionkova, 2007). The most prominent member of this group of natural products is podophyllotoxin (**1**) (Scheme 1). This compound, together with analogues (**2-4**) are aryltetralin lignan lactones isolated from the American Mayapple (*Podophyllum peltatum*) and related Indian species (*Podophyllum emodi*). Podophyllotoxin (**1**) has long been known to possess anti-mitotic activity with early clinical trials showing it to be highly efficacious but also quite toxic (Jardine, 1990), (Weiss et al., 1975) (Keller-Juslen et al., 1971). Four contiguous chiral centers contained within a stereochemically unstable trans-fused tetrahydronaphthalene lactone skeleton (Ward, 1982) are present in this compound.

Scheme 1



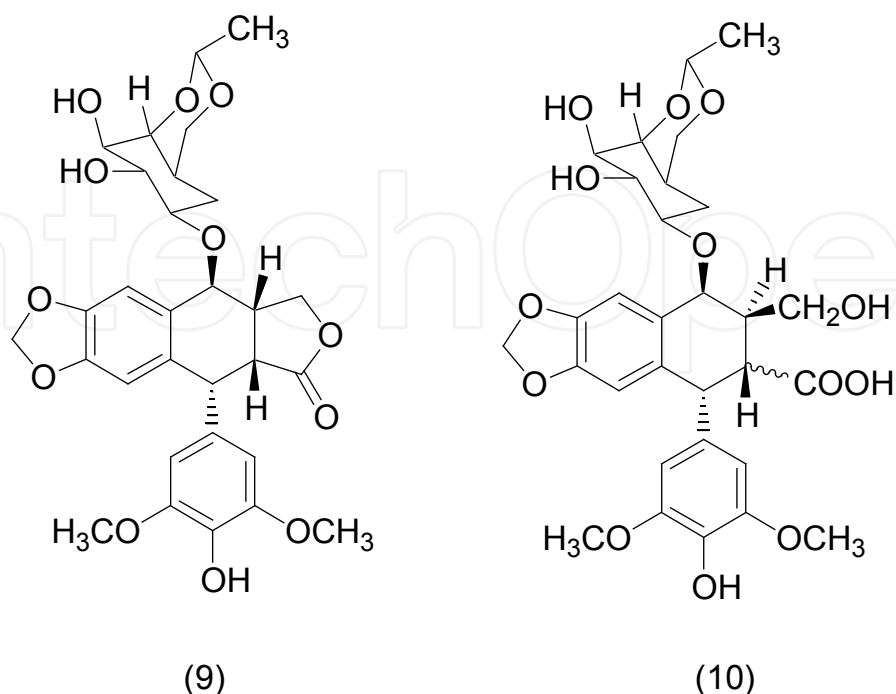
Scheme 2



A number of modifications have been done on podophyllotoxin structure (Damayanthi & Lown, 1998), and some of the congeners exhibit a potent antitumor activity. In fact, etoposide (5), teniposide (6), etopophos (7), GL-331 (8) (Kuo Hsiung-Lee, 2000) (Scheme 2) are potent chemotherapeutic agents for a variety of tumors. However, neither is optimal. For example, etoposide (5) and its analogues suffer from poor solubility and growing drug resistance. Consequently, further analogues continue to be described. GL-331 (8) is currently undergoing phase II clinical trials and has been shown to be more potent than etoposide as a topoisomerase II inhibitor and, more notably, has overcome multidrug resistance in cancer cells, including etoposide-resistant cancer cells (Xiao et al., 2004).

In vivo studies have shown that metabolic deactivation of etoposide occurs through two key pathways, giving metabolites (9-10) (Cragg & Suffness, 1988) (Dow et al., 1982) (Creaven, 1982) (Scheme 3).

Scheme 3



Epimerisation of the *trans* lactone to the *cis* isomer (**9**) leads to a 100-fold loss in activity. Hydrolysis of the lactone with concomitant epimerisation leads to the hydroxy acid (**10**), which is 500-fold less active than etoposide. It can be deduced from these two observations that the stereochemistry surrounding the C ring of podophyllotoxin (**1**) is critical for the overall activity of the molecule.

3. Antitumour Aryltetralines: Pharmacology

Lignans, and especially cyclolignans, have been the objective of numerous studies focused on preparing better and safer anticancer drugs (Gordaliza et al., 2000).

Etoposide (VP-16) and teniposide are currently in clinical use in the treatment of many cancers, particularly small cell lung carcinoma (SCLC), testicular cancer and malignant lymphoma.

Etoposide gained FDA approval in 1983 and in 1987 a soft gelatin capsule formulation was approved as well, which allowed long-term and more tolerable drug administration.

Clinical trials with etoposide began in 1971 and demonstrated its antineoplastic activity in AML (acute myeloid leukemia) (Kell, 2006), Hodgkin's disease (Advani & Horning, 2006), non-Hodgkin's lymphoma (Kluin-Nelemans et al., 2001), lung cancer, gastric cancer, breast cancer and ovarian and testicular cancer (Bookman et al. 2006).

This semisynthetic derivative, along with teniposide, is usually administered in combination chemotherapy in the treatment of lung cancer (both small cell and non-small cell), testicular cancer and in acute leukaemias. Apart from ovarian and testicular cancer, etoposide has also been tried in other solid tumours including those of the brain and thymus and also in the treatment of Kaposi's sarcoma associated with AIDS (Martindale, 2007).

In particular, cisplatin or carboplatin with etoposide remains the current standard chemotherapy regimen for small cell lung carcinoma, which accounts for about 10-20% of all lung cancers (Yee et al., 2008) and is the most aggressive form of lung cancer, with an overall 5-year survival less than 5%.

Germ cell tumours are the most common solid malignancies to affect young adult men and their incidence is increasing worldwide (Hussain et al., 2008). Advanced testicular cancer is successfully treated with etoposide, in combination chemotherapy with cisplatin and bleomycin (Feldman et al., 2008).

The dose-limiting toxicity of etoposide is myelosuppression, mainly seen as leucopenia, but also thrombocytopenia and sometimes anaemia. The nadir of the granulocyte count usually occurs 7 to 14 days after a dose, with recovery by about 21 days. Nausea and vomiting are common and gastrointestinal toxicity may be more common after oral dosage. Reversible alopecia occurs in about two-thirds of all patients. Hypersensitivity or anaphylactoid reactions can occur, characterized by flushing, chills, fever, tachycardia, bronchospasm, dyspnoea and hypotension. Peripheral or central neuropathies have been rarely observed. Tumor lysis syndrome has been reported after the use of etoposide with other chemotherapeutic drugs. Disturbances of liver function have been reported, mainly at high doses, and there have been occasional reports of cardiotoxicity.

Pharmacokinetic parameters determined from studies have shown that the area under the concentration versus time curve (AUC) and peak plasma concentrations achieved following i.v. etoposide administration are linearly related to dose (Hande et al., 1984). Etoposide's steady-state volume of distribution ranges from 5 to 171/m². Etoposide is highly bound to plasma proteins with an average free plasma fraction of 6%. Total etoposide clearance is modestly decreased in patients with renal failure, but not in patients with hepatic obstruction. The etoposide plasma binding ratio (the amount of bound drug/the amount of free drug) is directly related to the serum albumin concentration. Cancer patients, in particular those with hepatic involvement, often have reduced serum albumin concentrations. Since free etoposide is biologically active, conditions which decrease protein binding increase the pharmacological effect of a given dose.

The bioavailability of oral etoposide, ranges from 40 to 75%, changes with the drug dose and shows a considerable interindividual variability has been reported.

As etoposide is poorly soluble in water, the intravenous administration of large doses of the drug may require the administration of significant fluid volumes, and this fluid load can cause heart failure in some patients (Hande, 1998). Hypersensitivity reactions and hypotension may also occur with rapid administration of etoposide, perhaps due to the vehicles needed as solubilisers. To overcome solubility problems, etoposide phosphate (Etopophos®, Bristol-Myers Squibb Co), an etoposide prodrug for intravenous use, was produced and was approved by the FDA in 1996.

Etoposide phosphate can be administered more rapidly and seems to be associated to a reduced number of hypersensitivity reactions (Collier et al., 2008). This compound is soluble in water at concentrations up to 20 mg/ml. Several studies have shown that etoposide phosphate is rapidly and completely converted to etoposide by the action of alkaline phosphatases in blood, and it can be administered over short (5-30 min) time periods, is pharmacokinetically equivalent to etoposide and has identical toxicity. Conversion to etoposide is rapid and not saturated even at high drug doses (1.6 g/m²) used in marrow transplantation regimens.

In patients with high risk or relapsed lymphoma, high-dose etoposide phosphate proved to be bioequivalent to high-dose etoposide (Reif et al., 2001). The compound showed an acceptable toxicity and is successfully used with carboplatin in elderly patients with small-cell lung cancer (Quoix et al., 2001).

Teniposide was approved for clinical use in the US in 1993 and it is used primarily in the treatment of leukemias and lymphomas, mainly in childhood. Its toxicity is identical to those of etoposide. It can induce myelosuppression, hair loss, nausea, mild vomiting and mucositis, along with occasional hypersensitivity reactions.

4. Antitumour Aryltetralines: Mechanism of action

The mechanism by which the aryltetralin lignan podophyllotoxin (**1**) blocks cell division is related to its inhibition of microtubule assembly into the mitotic apparatus. However, etoposide and teniposide were shown not to be inhibitors of microtubule assembly. This suggested that their antitumor properties were due to another mechanism of action: their interaction with DNA. In fact, they induce a block in late phase S or early G2 by interacting with the enzyme topoisomerase II (Botta et al., 2001).

DNA topoisomerases are nuclear enzymes which make transient DNA strand breaks, allowing the cell to manipulate the topology of its DNA. These enzymes are essential for DNA replication, transcription, chromosomal segregation and DNA recombination. They act by cleaving one or both DNA strands, allowing the passage of an unbroken strand or DNA duplex through the breakage site prior to resealing the break. As a result of their double-stranded DNA passage reaction, type II topoisomerases are able to regulate over- and under-winding of the double helix and resolve nucleic acid knots and tangles.

It was not until 1979 that the name “DNA topoisomerases” was introduced. Extensive biochemical analysis of this group of enzymes was undertaken at the same time etoposide was brought to the clinic.

Etoposide was the first agent recognized as a topoisomerase II inhibiting anticancer drug; in 1984, several laboratories demonstrated that mammalian topoisomerase II was the target for etoposide action.

This compound and other topoisomerase II inhibitors do not kill cells by blocking topoisomerase catalytic function. They poison these enzymes by increasing the steady-state concentration of their covalent DNA cleavage complexes. This action converts topoisomerases into physiological toxins that introduce high levels of transient protein-associated breaks in the genome of treated cells.

The potential lethality of these drug-induced cleavage complexes rises dramatically when replication machinery or helicases attempt to traverse the covalently bound topoisomerase roadblock in the DNA. This disrupts the cleavage complex and converts transient single- or double-strand breaks into permanent double-stranded fractures which are no longer held together by proteinaceous bridges. These breaks become targets for recombinations, sister chromatid exchange, the generation of large insertions and deletions and the production of chromosomal aberrations and translocation. When these permanent DNA breaks are present at sufficient concentration, they trigger a series of events that ultimately culminate in cell death by apoptosis.

As most topoisomerase II inhibiting agents are substrates for P-glycoprotein or other multidrug resistance associated proteins, the development of newer and better

podophyllotoxin-based strategies for the treatment of malignant disease may be forthcoming (Liu et al., 2007).

Other podophyllotoxin derivatives which retain or even improve the cytotoxic activity have been studied, but these are weak inhibitors of topoisomerase II *in vitro*; the data revealed that such analogs exhibit a different, as yet unknown, mechanism of action. The main deficiency of these compounds is their cytotoxicity for normal cells and hence the side effects derived from their lack of selectivity against tumoral cells. With this regard it is necessary to investigate and prepare new more potent and less toxic analogs, with better therapeutic indices.

5. Synthetic Routes

Since its first isolation in 1953 (Hartwell et al., 1953), podophyllotoxin (**1**) and its isomers have been the subject of numerous synthetic endeavours (Pelter et al., 1998), (Ward 1990, 1992, 2004).

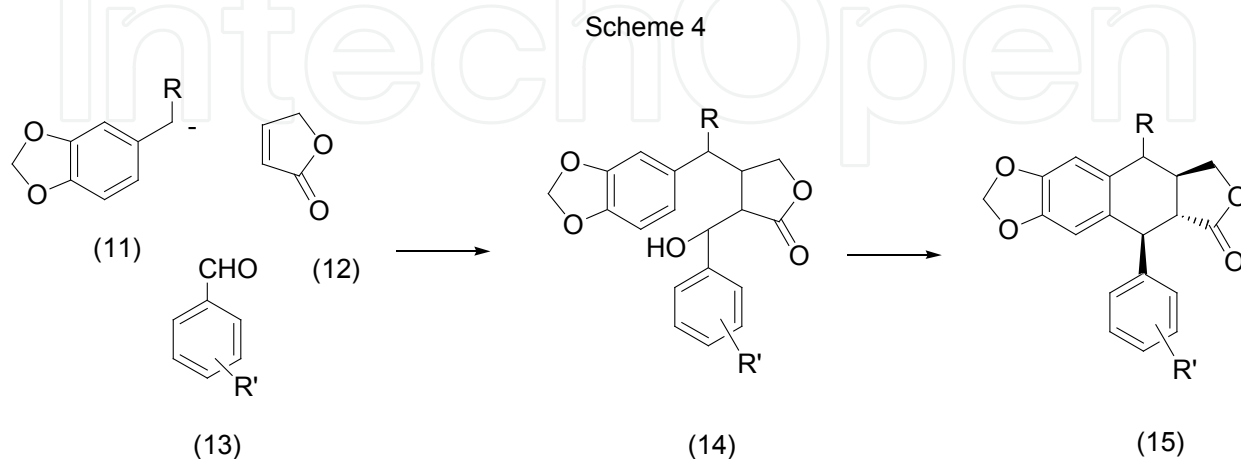
The particular challenge for podophyllotoxin (**1**) is in establishing the 1,2-*cis* stereochemistry together with a *trans* lactone ring fusion (Sellars & Steel, 2007). Because of the different stability of the stereoisomers, on mild base treatment, podophyllotoxin undergoes rapid epimerisation to afford a 97.5:2.5 mixture of picropodophyllin and podophyllotoxin (Gensler & Gatsonis, 1966).

PM3 calculations show in fact that podophyllotoxin and GL-331 are 1.1 kcal/mol more stable than isopodophyllotoxin and iso-GL-331 respectively (Rindone, 2009).

a) C-Ring Formation by Aryl Substitution

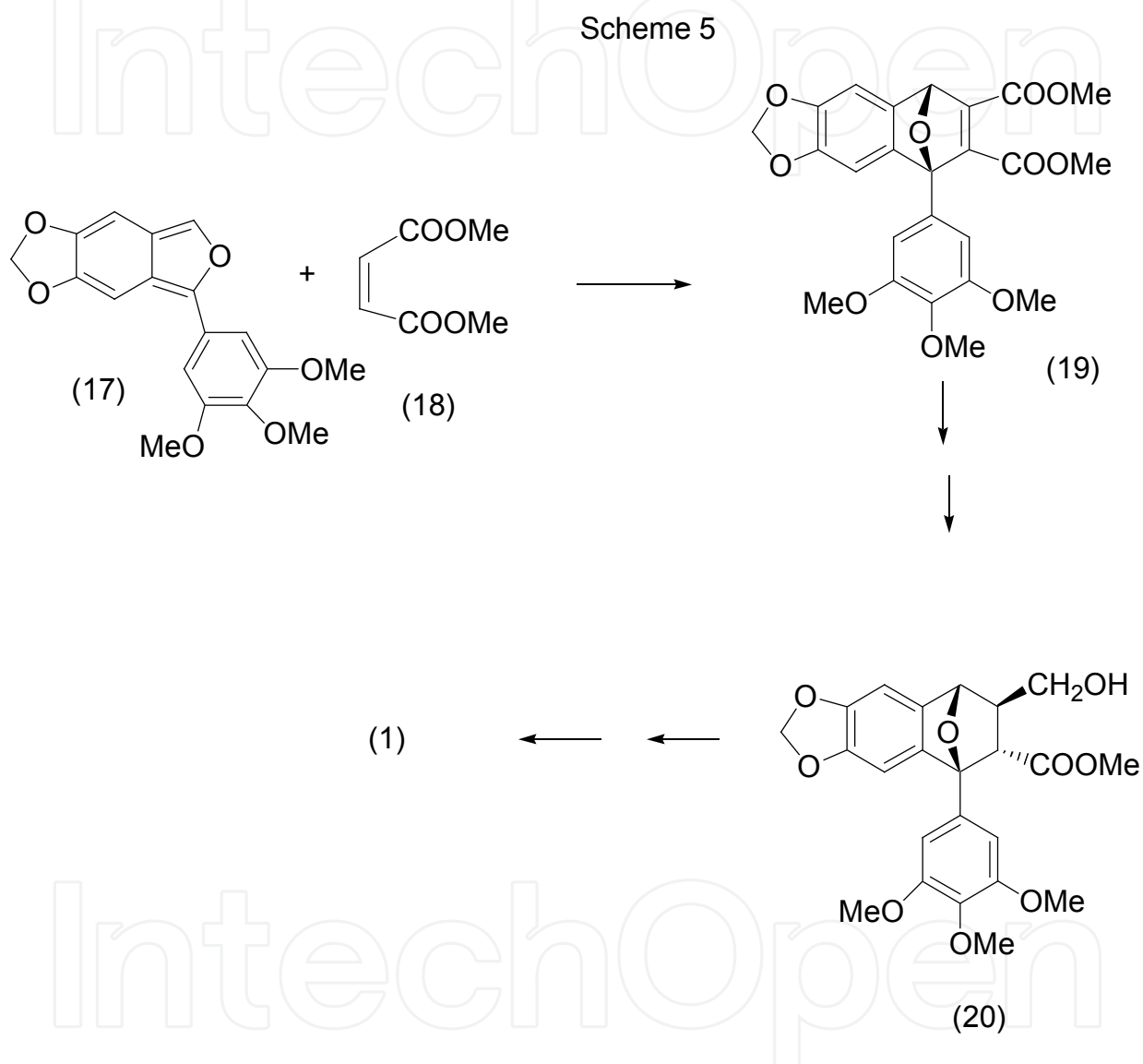
The most common approach for the aryltetralin lactone skeleton is the electrophilic aromatic substitution forming the C1-C6 bond and simultaneously establishing the stereochemistry at C1. A three-component coupling strategy for aryltetralin lignan lactone synthesis is shown in Scheme 4.

This involves an acyl anion equivalent (**11**), a butenolide Michael acceptor (**12**) and an aldehyde (**13**). Intermediate (**14**) is formed and is cyclised to compound (**15**), having a 1,2-*trans*,2,3-*trans* stereochemistry (Pelter et al, 1990), (Gonzales et al., 1978) (Van Speybroek et al. 1991).



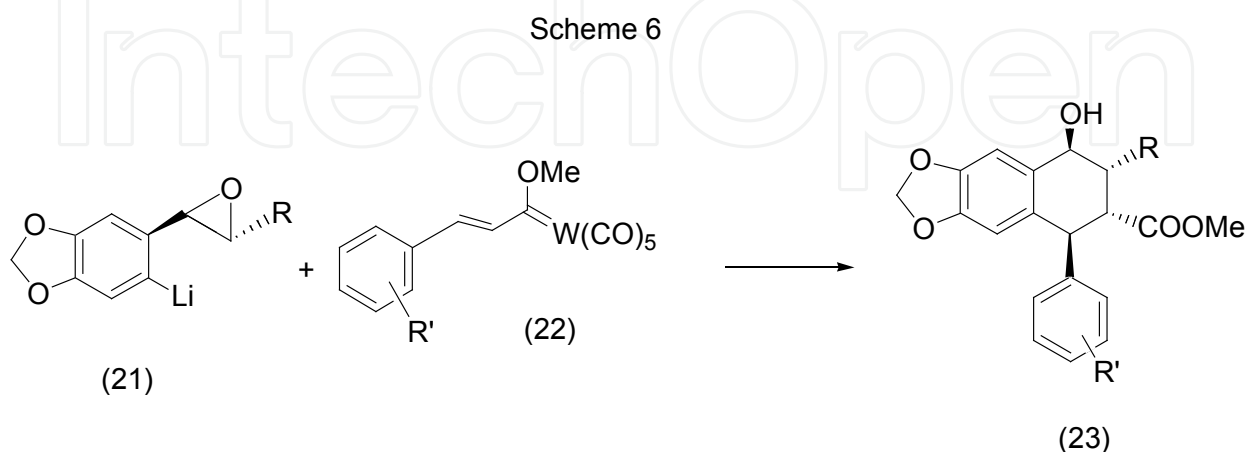
b) C-Ring Formation by Cycloaddition Reactions

The other principal strategy for the construction of the cyclic system is the Diels–Alder reaction. The oxabicyclo adduct **(19)** derived from the isobenzofuran **(17)** and dimethylmaleate **(18)** gives an intermediate **(20)** which is further transformed into podophyllotoxin **(1)** (Rodrigo, 1980), (Rajapaksa & Rodrigo, 1981) (Forsey et al., 1989), (Jones et al., 1987), (Kuroda et al., 1996) (Scheme 5).

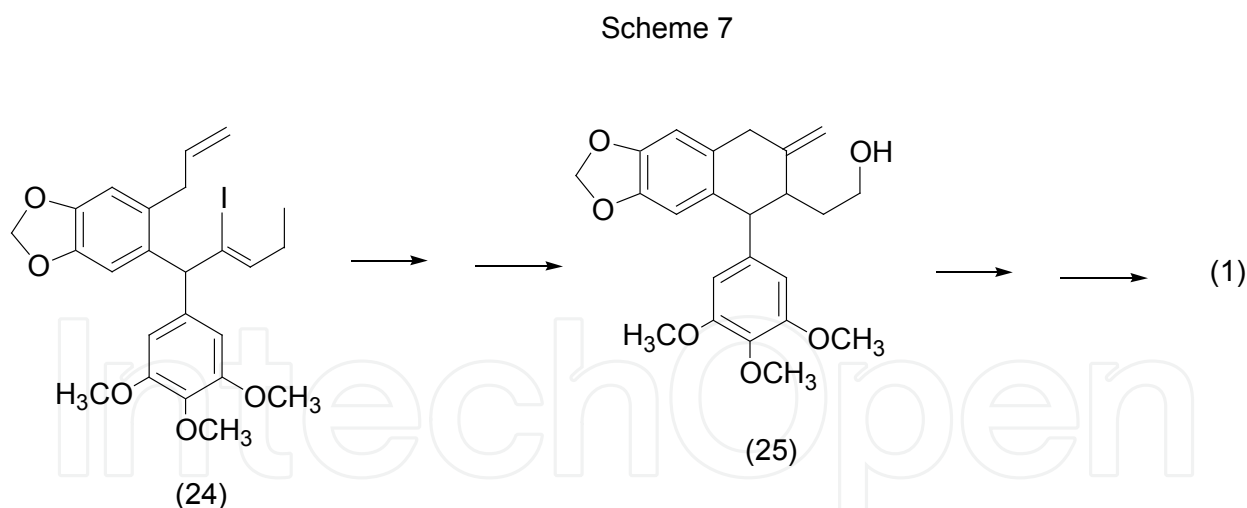


c) C-Ring Construction via Michael Induced Ring Closure

The application of a Michael-induced ring-closure using a chiral intermediate gives the formation of the *1,2-trans* stereochemistry. One example is the reaction of a tungsten-carbene (**22**) with the chiral methylenedioxyalkylstyrene epoxide (**21**) to form a reaction product (**23**) having a *1,2-trans,2,3-cis* stereochemistry (Kende et al., 1981), (Capriati et al., 2005) (Scheme 6).



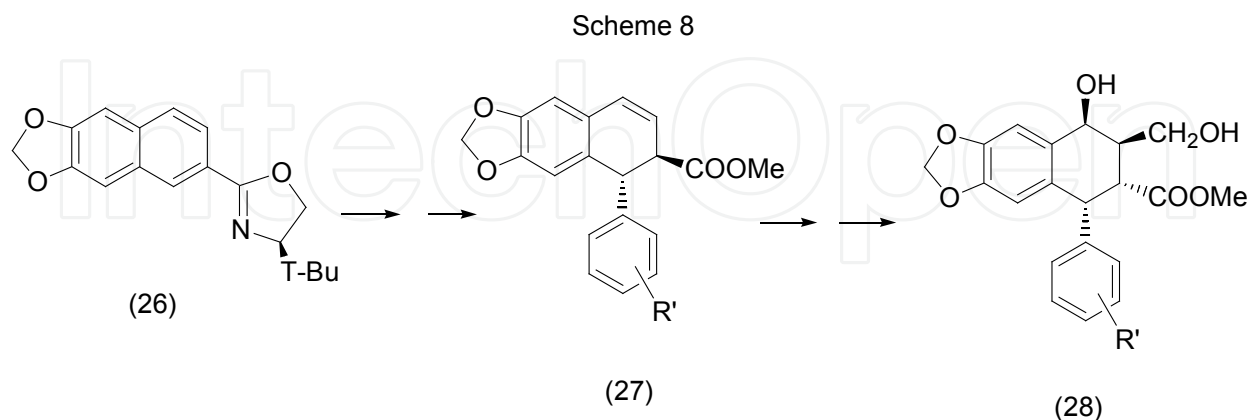
Alternatively, an intramolecular Heck reaction starting from the iododerivative (**24**) forms compound (**25**), subsequently transformed into podophyllotoxin (**1**) (Kennedy-Smith et al., 2004) (Scheme 7).



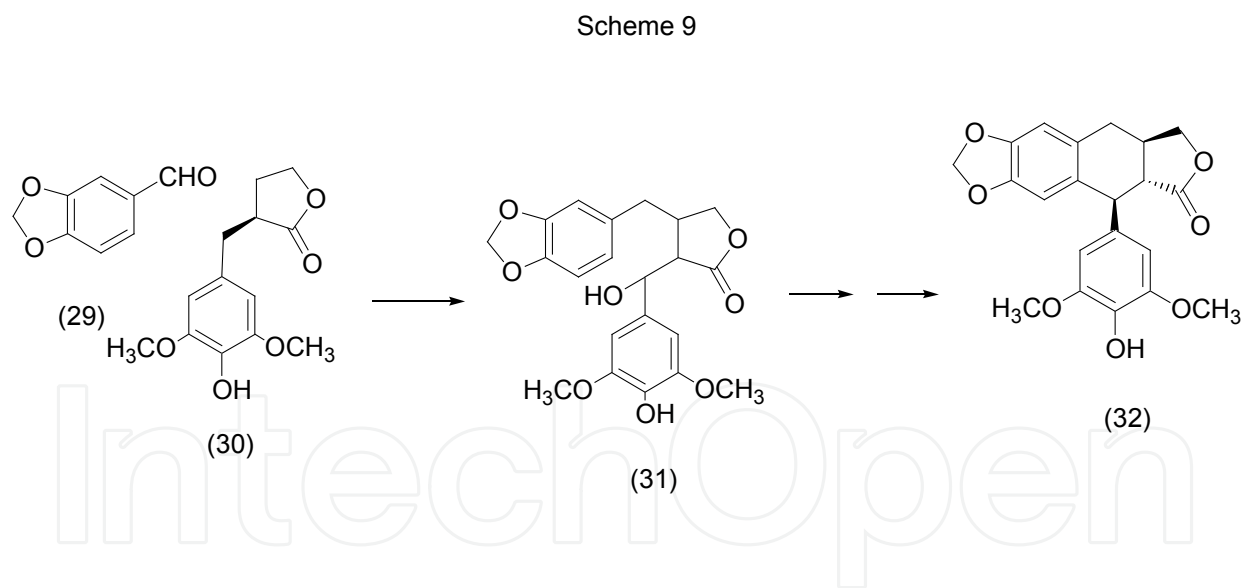
d) The use of chiral auxiliaries

Some other synthetic pathways have been performed introducing in the molecule a chiral auxiliary intended to drive the formation of the stereogenic centers in reactions performed using the methodologies exposed in the preceding paragraphs.

d1): The enantioselective dearomatisation of a naphthalene derivative **(26)** resulted in the generation of the *1,2-trans* stereochemistry in **(27)** which may be converted into **(28)**, having *1,2-trans,2,3-cis* stereochemistry (Scheme 8) (Andrews et al, 1988).

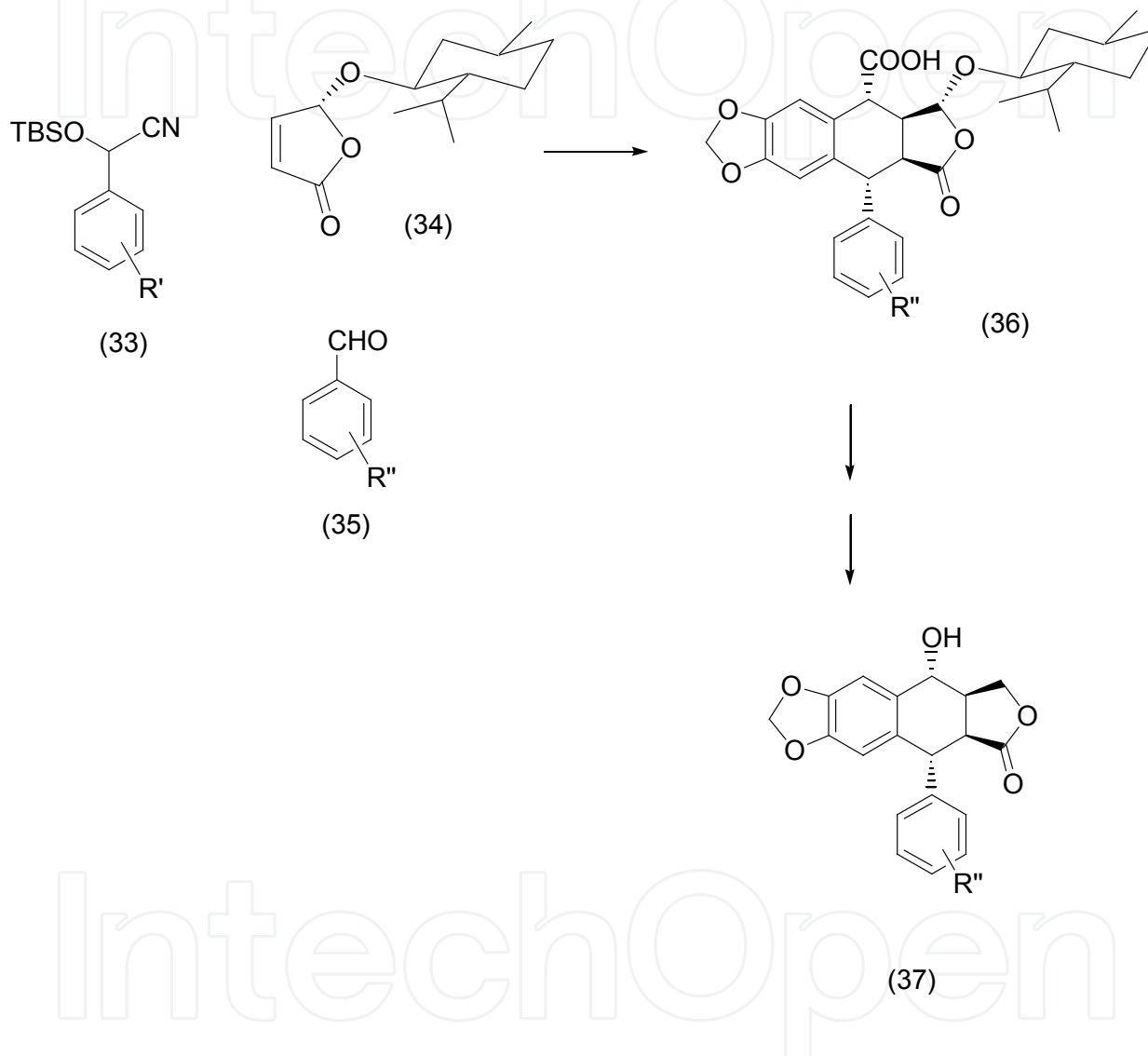


d2): The condensation of a chiral benzyl- γ -butyrolactone **(30)** with piperonal **(29)** gives compound **(31)**. Subsequent alkylation and cyclization gives demethyldeoxyisopodophyllotoxin **(32)**, having a *1,2-trans,2,3-trans* stereochemistry (Engelhardt et al. 2003) (Scheme 9).



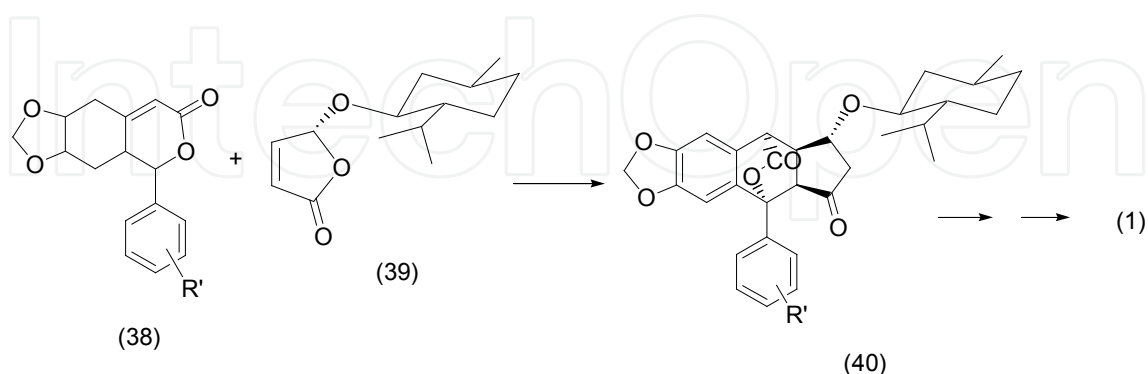
d3): The conjugate addition of the menthyl derivative (34) with the benzyl cyanide (33) and a substituted benzaldehyde (35) gave intermediate (36). Removal of the menthyl fragment resulted in the formation intermediate (36) and then of aryltetraline (37) with a 1,2-*trans*, 2,3-*cis* stereochemistry (Ward et al., 1998) (Scheme 10).

Scheme 10



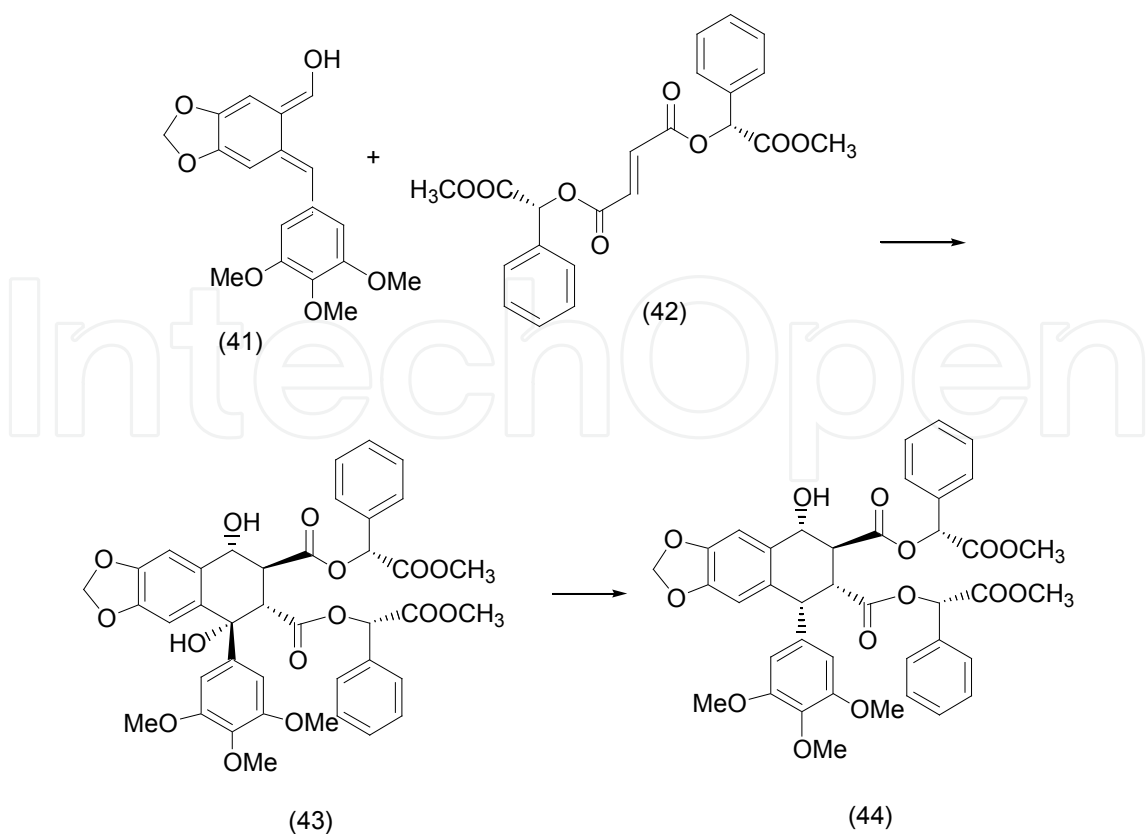
d4): Menthylloxymethoxyfuranone (**39**) and pyrones (**38**) gave the *endo* adduct (**40**) which was transformed into podophyllotoxin (**1**) with 1,2-*cis*-2,3-*trans* stereochemistry by acid-promoted elimination of the lactone bridge in intermediate (**40**) (Bush & Jones, 1996) (Scheme 11).

Scheme 11



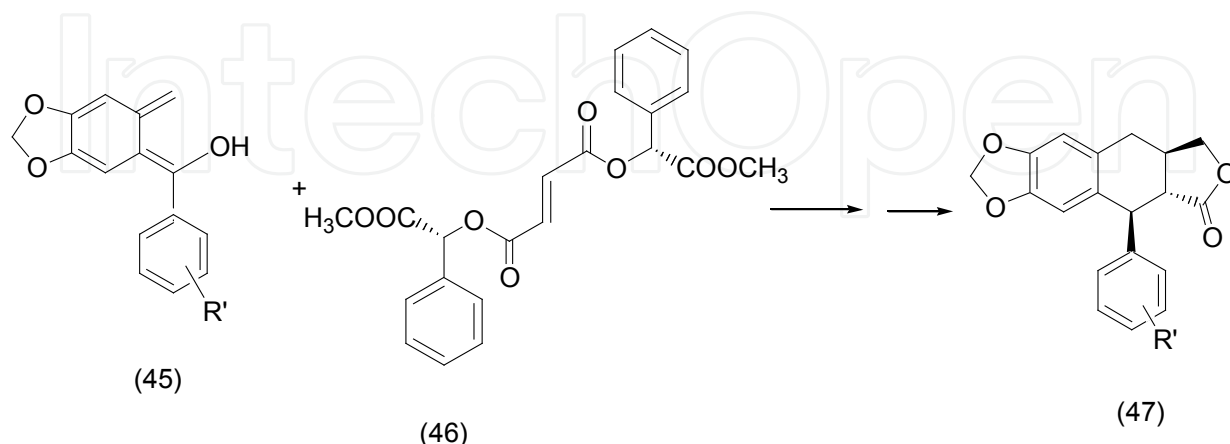
d5): A Diels-Alder cycloaddition between the fumarate of methyl (*S*)-mandelate (**42**) and α -hydroxy- α -aryl-o-quinodimethane (**41**) produces an *endo* cycloadduct (**43**) which may be converted into optically pure (-)-deoxypodophyllotoxin (**44**) having 1,2-*cis*,2,3-*trans* stereochemistry (Bogucky & Charlton, 1995) (Scheme 12).

Scheme 12



d6): A Diels-Alder cycloaddition between the fumarate of methyl (S)-mandelate (**46**) and α -hydroxy- α' -aryl-o-quinodimethane (**45**) gives optically pure (-)- α -dimethylretrodendrin (**47**) having a 1,2-*trans*-2,3-*trans* stereochemistry, and three of its diastereomers (Scheme 13) (Charlton et al., 1990), (Charlton & Koh, 1992), (Maddaford & Charlton, 1993).

Scheme 13



6. The biomimetic strategy

One alternative is the biomimetic pathway, using the oxidative phenol coupling reaction which is the strategy the cell uses for the biosynthesis of lignans.

Recently Lewis has proposed a new biosynthetic pathway to enantiopure lignans. A protein isolated from *Forsythia* species is suggested to be responsible for the formation of enantiomeric pure pinoresinol from coniferyl alcohol (Lewis & Davin, 1999). In this case, the protein acts as a chiral inducer. The role of the directing protein is supposed to be at the level of 8-8 coupling of phenols.

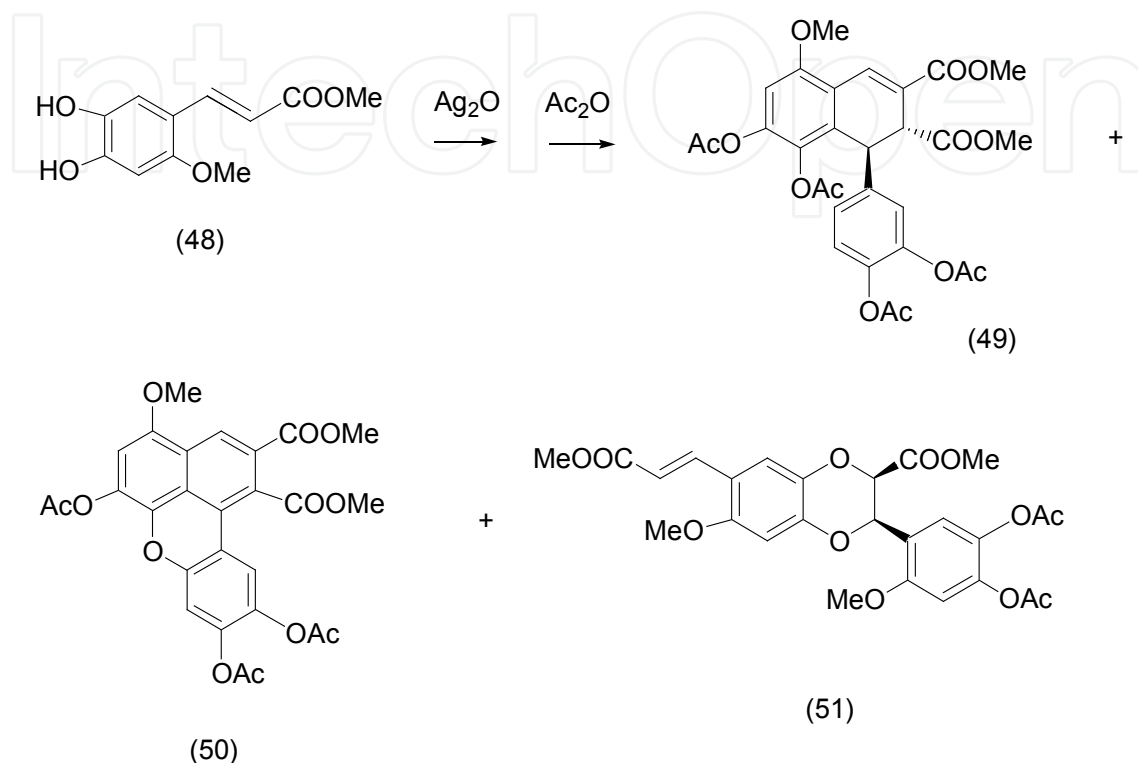
The *in vitro* bimolecular phenoxy radical coupling reaction is not under a strictly regio- and stereospecific control. This is due to the fact that phenoxy radicals are very persistent and the dimerization reaction is slow. Hence the stereogenic carbons formed in the oxidative phenol coupling reaction *in vitro* are racemic. Sarkanen has studied the radical phenol coupling since 1973 and he has demonstrated that the 8-8 coupling of phenols such as (*E*)-isoeugenol is remarkably stereospecific and produces exclusively *threo* compounds, whereas (*Z*)-isoeugenol gives *threo*- and *erythro*-coupling products in equal amounts. He has proposed that the differences in the probabilities of coupling modes in the oxidations of (*E*) and (*Z*)-isoeugenol must be considered to be due to the characteristics of these intermediate complexes rather than to the differences in spin densities (Sarkanen & Wallis, 1993).

The enzymatic oxidative coupling of ferulic acid derivatives was observed by us to result in the diastereoselective synthesis of benzo[b]phenylcoumarans (Bolzacchini et al., 1998). Stereocontrol in this reaction to enantioselectively give benzo[b]phenylcoumarans has been recently shown by us to be possible (Rummalko et al., 1999) using a chiral inducer and the horseradish peroxidase (HRP)-catalyzed oxidative coupling in presence of hydrogen peroxide as the oxidant. The chiral inducers were aminoacid ethyl esters, camphorsultam and aryloxazolidinones (Bruschi et al., 2006).

6.1 Metal-mediated oxidative phenol coupling

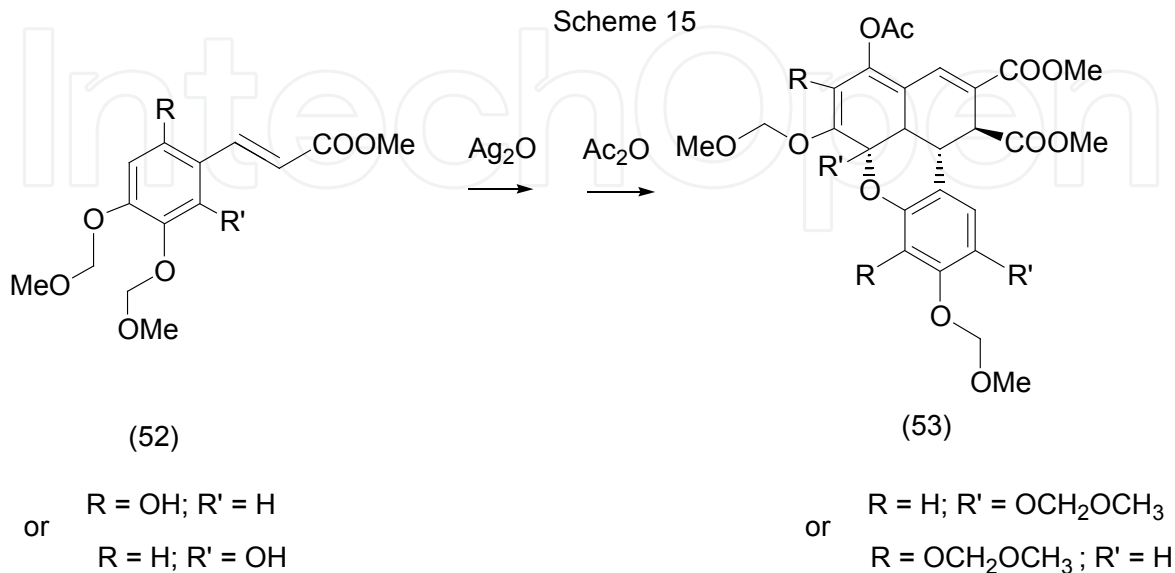
a): The oxidative phenol coupling of compound **(48)** with silver oxide gave, after acetylation, a mixture of the aryltetraline **(49)**, with a *1,2-trans* stereochemistry and a 3,4 double bond, the benzo[*kl*]xanthene **(50)** and the benzodioxane **(51)** (Maeda et al., 1994) (Scheme 14).

Scheme 14



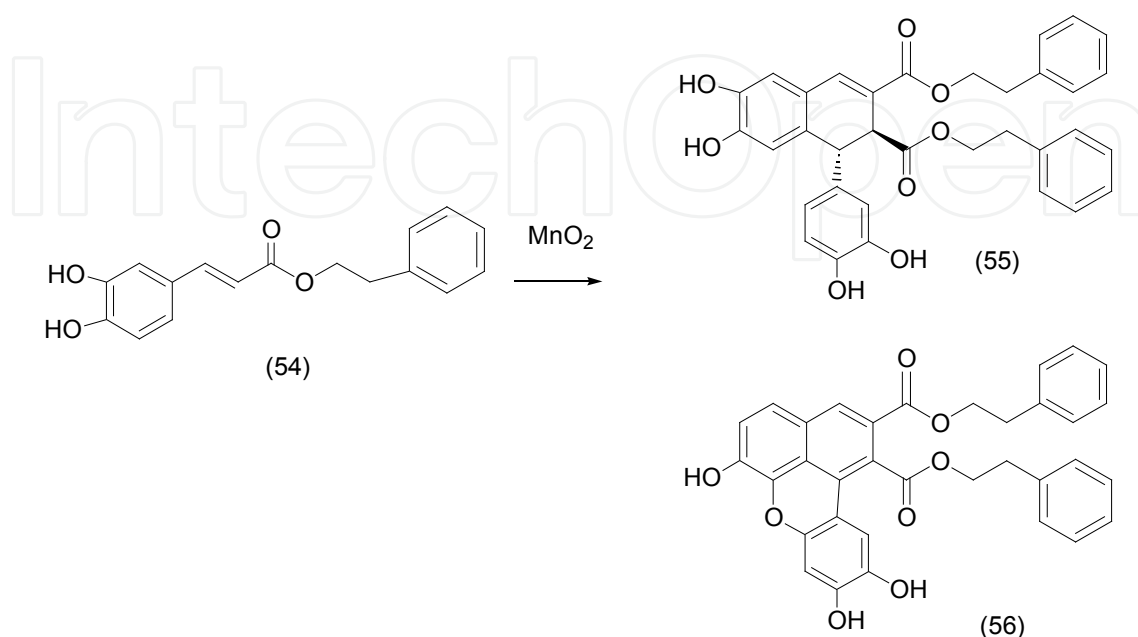
b:) 2-hydroxycinnamates **(52)** underwent oxidative phenol coupling with silver oxide to give, after acetylation, compound **(53)** (Maeda et al., 1995) having *1,2-trans* stereochemistry and a 3,4-double bond (Scheme 15).

Scheme 15



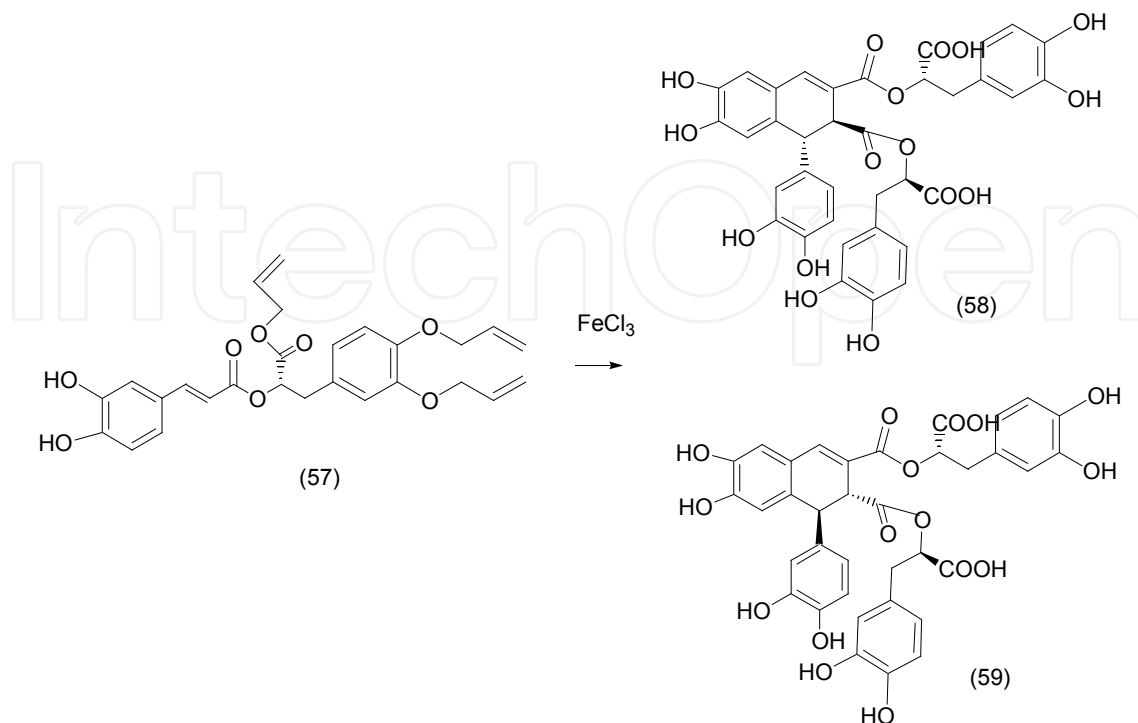
c:) With MnO_2 , the oxidative phenol coupling using compound **(54)** as the starting material gave the aryltetralin **(55)** having a 1,2-*trans* stereochemistry and a 3,4-double bond and the benzo[*kl*]xanthene **(56)** (Scheme 16) (Daquino et al., 2009).

Scheme 16



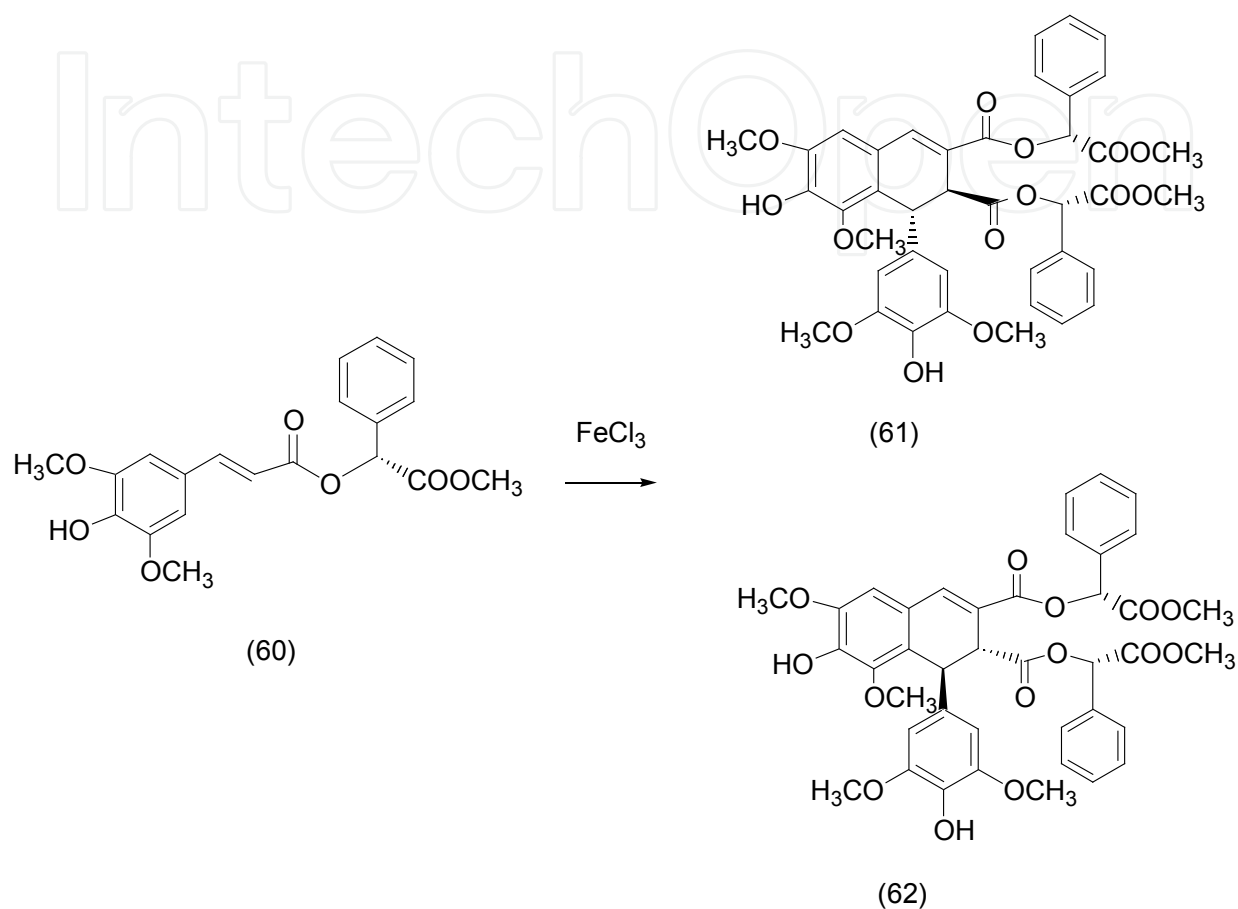
d:) The triallyl derivative of (S)-rosmarinic acid **(57)** was submitted to FeCl_3 -assisted oxidative phenol coupling forming the diastereoisomers **(58-59)** of radosiin, having a 1,2-*trans* stereochemistry and 3,4-double bond (Bogucki & Charlton, 1997) (Scheme 17).

Scheme 17



e:) (R)-mandelyl sinapate (**60**) was diastereoselectively transformed by FeCl_3 -assisted oxidative phenol coupling into trans-thomasidioate diester (**61-62**), having a 1,2-*trans* stereochemistry and a 3-4 double bond (Bogucki & Charlton, 1997) (Scheme 18).

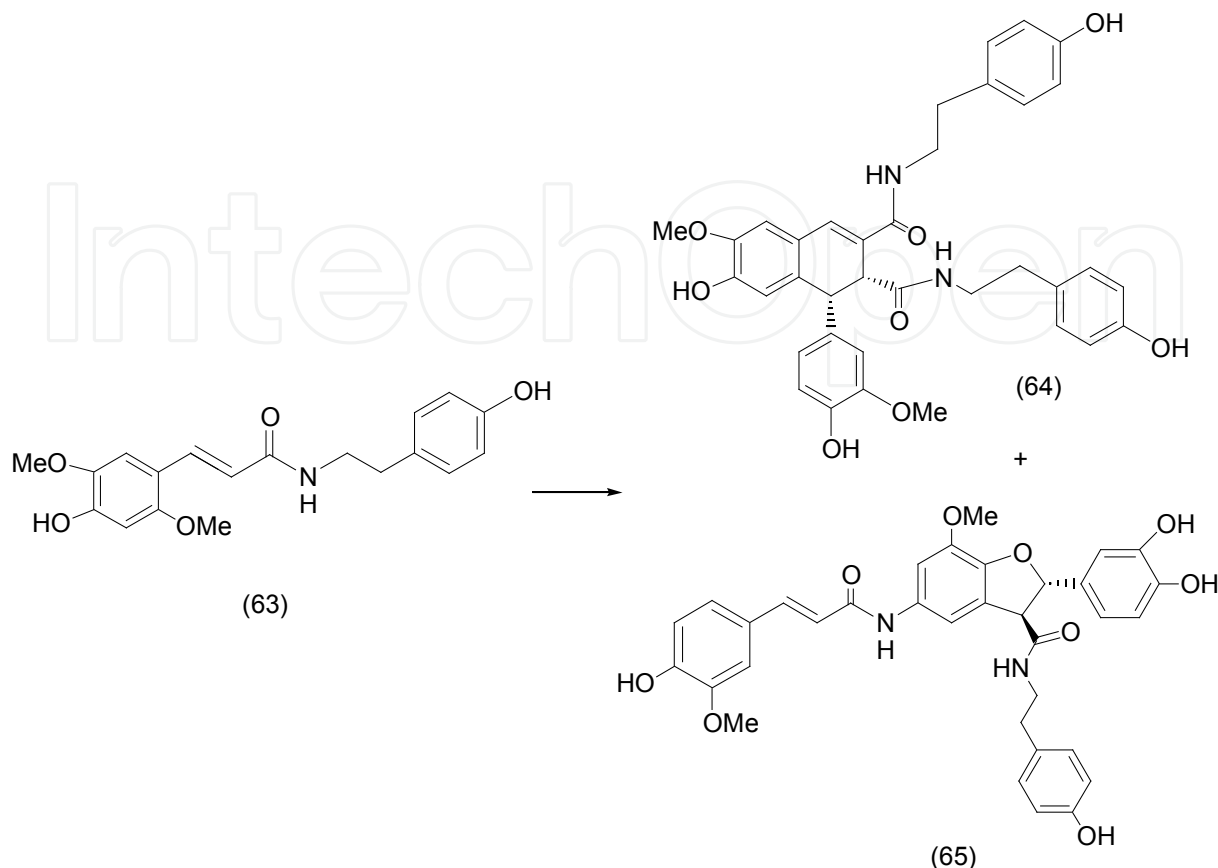
Scheme 18



6.2 Enzyme-catalyzed oxidative phenol coupling

a:) Amide (**63**), submitted to oxidative phenol coupling with hydrogen peroxide in the presence of horseradish peroxidase gave a mixture of the levorotatory isomer of the aryltetraline cannabisin (**64**), having a 1,2-*cis* stereochemistry and a 3,4 double bond, and the phenylcoumaran grossamide, (**65**) (Scheme 19) (Lajide et al., 1995).

Scheme 19



b.) The enantioselective oxidative phenol coupling of sinapic acid derivatives (**66**) (Scheme 18) having an amide bond with (*S*)-phenylalanine ethyl ester, (*S*)-methylbenzylamine, (*S*)-2-phenyloxazolidinone as chiral auxiliaries was performed using hydrogen peroxide as the oxidant and horseradish peroxidase as the catalyst (Zoia et al., 2008).

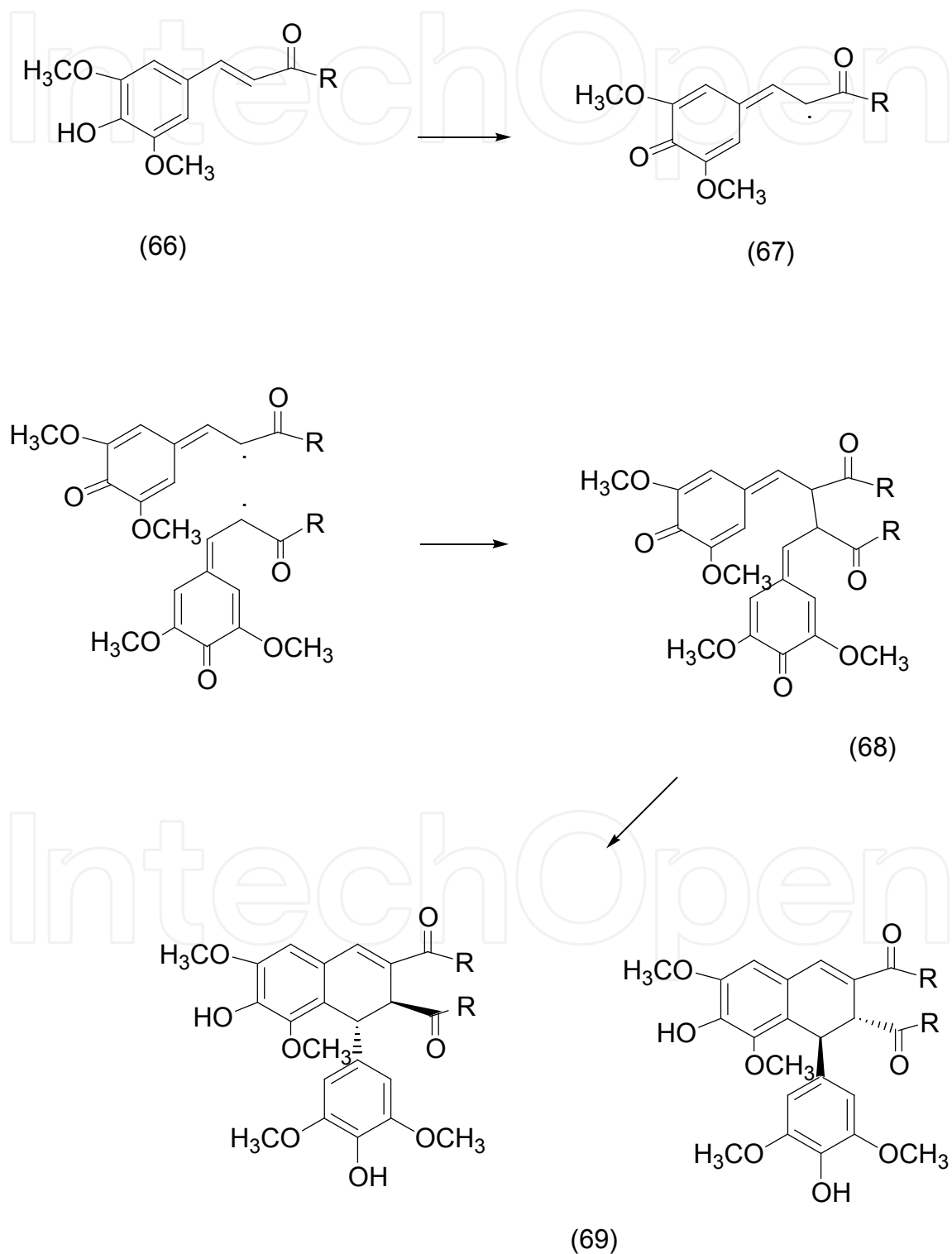
The proposed reaction pathway involves two steps; the first step is the 8-8 oxidative coupling of two phenoxy radicals (**67**) to give the bisquinomethide (**68**), and the second step is the ring closure of (**68**) to give the final product. For this mechanism the absolute configuration of thomasidioic acid amide (**69**) should be determined by the absolute configuration of the two stereogenic centers of the bisquinomethide (**68**) formed in the 8-8 oxidative coupling, and by its *trans* or *cis* ring closure (Scheme 20).

The computed profile along the reaction pathway for the 8-8 coupling at the *re-re*, *si-si*, and *re-si* faces shows that the energy barrier calculated for the *si-si* coupling is higher by more than 4 kcal mol⁻¹ than that calculated for the *re-re* and *re-si* coupling. This result suggests that the formation of the *R,R* (from *re-re* coupling), and *R,S/S,R* (from *re-si* coupling) bisquinomethide (**68**) is preferred with respect to the formation of the *S,S* (from *si-si* coupling) bisquinomethide (**68**).

The cyclization step determines the observed diastereoselection to the *trans* isomer. The diastereoselection should be controlled by the relative orientation of the two quinomethide rings which should feature a preferred conformation in order to give the "correct" ring closure, as well as to the energy of the transition state along the reaction path to give the final product.

A conformational analysis was performed in order to predict the enantioselectivity in the formation of *trans*-thomasidioic acid amide (69) from quinomethide (68) having a (*S*)-2-phenyloxazolidinone chiral auxiliary group.

Scheme 20



Our computational investigation of the 8-8 oxidative coupling of quinomethide radical (67) shows that the *R,R*, *S,S* and *R,S*, *S,S* isomers of bisquinomethide (68) should be formed in larger amounts with respect to the *S,S*, *S,S* isomer. The former, after aromatization preserves only one *R* centre that gives ring closure to the *trans* 1*S*,2*R* absolute configuration, while the latter after aromatization can preserve both an *R* or *S* centre, giving ring closure to both the *trans* 1*S*,2*R*, and 1*R*,2*S* absolute configurations. Hence, the configuration of thomasidioic acid amide (69) from this enantioselective synthesis is predicted to be 1*S*,2*R*.

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